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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 11/00)

1- File Copy

Office Action Summary	Application No. 09/479,862	Applicant(s) OKURA ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,9,12,15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,9,12,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/884,324* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of the invention of group III (claims 3, 9, 12, 15, and 17) in Paper No. 9 is acknowledged.

2. Claims 1, 2, 4-8, 10, 11, 13, 14, and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

3. Regarding the foreign priority, it is noted that the Applicants have indicated in the transmittal sheet of papers filed 1-10-00 that the priority documents are present in the parent case Application No. 08/884,324.

Information Disclosure Statement

4. The information disclosure statement filed 1-10-00 is acknowledged. However, the references have not been considered because they seem to have been misplaced in the office. Applicants' help in getting a copy of all the references listed in the above IDS is appreciated.

Specification

5. The disclosure is objected to because of the following informalities: Text is missing in line 25 on page 13 and line 2 on page 27.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 3, 9, 12, 15, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As instantly recite, claimed invention is drawn to an ex vivo method of treating any tumor in a subject by isolating tumor cells from the subject, transforming them with a genomic DNA or fragment thereof that encodes the amino acid sequence of SEQ ID NO 1, growing the transformed cells in culture and then implanting the transformed-cultured cells into the subject at any site. It is noted that SEQ ID NO 1 is the amino acid sequence of IL-18 or interferon-gamma inducing factor.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

In the instant case, the specification is not enabling for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have transplanted the cells transformed tumor cells into a subject so that the transplanted cells would have produced sufficient amount of IGIF or IL-18, secreted it out, and the secreted IL-18 would have been taken up by the cells in sufficient amount so that the tumor cells would have been killed, and an artisan of skill would have required to carry out extensive experimentation to practice the

claimed method and such would have been considered undue because the method of ex vivo gene therapy is unpredictable and the experimentation to address the unpredictability issues would not be routine.

The specification as filed describes a genomic DNA that encodes IGIF or IL-18 and that a vector comprising a genomic DNA under the control of CMV promoter can express the IL-18 protein in vitro in a CHO cell (see examples 2 and 3). Specification also discloses that the polypeptide produced by these cells induces IFN-gamma production by T cells (example 4-2). The specification on page 11, first full paragraph continued on page 12, discloses a general disclosure that the DNA of the invention can be used in gene therapy and ex vivo therapy, however, no examples of vectors, tumor cells, what dose of cells would be administered or any other description of the claimed method.

To practice the claimed method, an artisan would have to isolate tumor cells from a subject, transform them with a vector comprising the genomic DNA or a fragment of the genomic DNA that expresses the amino acid sequence of SEQ ID NO 1, grow the transformed cells in culture and then transplant them back at any site to treat any tumor. While the skill level of an artisan practicing the claimed invention would be high and such an artisan would have been able to isolate tumor cells from a subject and transform them with the expression vector whether the vector is a plasmid or a virus, the issue is: what vector would have been used, how would an artisan have transplanted the cells back in the subject, at what site in the subject and whether such transplanted cells would have produced IL-18 that would have been taken up by another tumor cell in sufficient amount to treat the tumor of the subject, whether any and all tumors could be treated, and whether IL-18 produced by cells isolated from one type of tumor could treat another type of tumor.

First, it is noted that the art of ex vivo gene therapy was unpredictable at the time of the invention and it is unpredictable even today. It is noted that for ex vivo gene therapy the most crucial step is expression of a gene of interest by a cell when transplanted in a subject in sufficient amounts and major hurdle in this step is a suitable vector.

At the time of the invention vector design and construction was unpredictable. Anderson (Anderson WF. Nature 392 (SUPP): 25-30, 1998) noted that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further added, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Even four years after the filing date of the claimed invention, that art of gene therapy remains unpredictable. Romano et al., while reviewing the state of gene transfer technology, noted, "From this standpoint, despite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame" (Stem Cells 18: 19-39, 2000). There are limitations of different vector systems; for example, retroviral vectors can not be used in neuronal cells or hepatocytes. Investigators did not find any therapeutic efficacy when LDL receptor transgene carrying hepatocytes (isolated and transfected with the transgene) were infused into the liver, which indicated that transduction efficiency was not high or that transduced cells were lost or eliminated after infusion into the liver. In addition to this, there is the limitation of extrapolating results obtained in small animals to those in larger animals. For example, animal models showed efficient retroviral mediated gene transfer into the liver of rodents, but a poor efficacy of intervention was observed in larger animals such as dogs (see left column on page 24 in Romano et al.). These examples indicate the unpredictability of the therapeutic interventions of ex vivo gene therapy wherein a transgene is introduced into a cell using a retroviral vector. Similarly, adenoviral vectors are limited by immunogenicity, which is not only responsible for eliciting inflammatory and toxic reactions in the host, it also causes elimination of the viral vector before gene transfer could be carried out (see right column on page 27). AAV-based vectors on

the other hand have limitations of insertional mutagenesis, contamination with helper virus, and size of the transgene insert (see page 29). All these limitations make the ex vivo gene therapy further unpredictable. The specification does not provide any guidance as to how an artisan of skill would have addressed these limitations when practicing the claimed method.

In addition to the listed issues, the real issue is the production of sufficient amount of IL-18 when the cells are transplanted or reinfused in the subject. The specification does not provide any guidance whether IL-18 would have been produced by transplanted cells in vivo and whether there would have been any treatment of the tumor. Next the question is would IL-18 treat any and all tumors? Golab (Cytokine 12:332-338, 2000) reviewed the state of the art of IL-18 in tumor immunotherapy and noted that IL-18 NK mediated antitumor effects against IP growing Meth A sarcoma but not with Ehrlich ascites carcinoma. Furthermore, only IP or IV administered IL-18 was effective, while subcutaneously administered IL-18 was not effective. IL-18 did not affect the proliferation of tumor cells in vitro indicating an indirect activity (see last paragraph in left column on page 333). However, in transduction of human pancreatic carcinoma cells with IL-18 transgene did not produce antitumor effects in nude mice (see last paragraph in right column on page 334). These results therefore indicate that the antitumor effects of IL-18 is unpredictable even today, four years after the filing date of the instant invention. Furthermore, the study that supported the antitumor effects of IL-18 used protein administration, while the study that was unsuccessful used ex vivo method, which is similar to the instantly claimed method. Accordingly, in the absence of any supporting evidence and working example in the specification, an artisan would have not expected that the ex vivo method of treatment of a tumor using IL-18 would have worked and neither the specification nor the prior art teaches a method as to how an artisan of skill would have practiced the claimed invention. It is noted that the claimed method encompasses treatment of any tumor type when cells are administered or transplanted by any method or at any site. For example, it is not clear whether the method would have worked if the cells were transplanted at a site other than the tumor because IL-18 would have to be produced by the transplanted

cells, transported to a tumor, taken up by the IL-18 receptors of the tumor cells and produce therapeutic effect. Again, there is no evidence or disclosure whether IL-18 would have been produced in sufficient quantity so that they could reach farther sites and treat tumors. Furthermore, Golab noted that there was a difference in the anti-tumor effects of IL-18 on highly immunogenic tumors versus weakly-immunogenic tumors. Furthermore, there is no evidence that IL-18 had anti-tumor effects on metastasis of if a tumor cell isolated from one tumor type transformed with the genomic DNA encoding SEQ ID NO 1 when transplanted into a subject would have treated another type of tumor. In conclusion, in addition of the art of gene therapy being highly unpredictable in general, tumor therapy with IL-18 ex vivo with tumor cells (derived from a subject's tumor comprising a transgene expressing IL-18) is also highly unpredictable.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effects. In other words, an artisan of skill would have had to carry out extensive experimentation of trial and error to develop a suitable vector, a route of administration and the type of a tumor, in order to practice a method of treating a tumor of any type and such experimentation would have been considered undue because such experimentation would not have been routine due to the unpredictability of the method of gene therapy in general and of the ex vivo method of therapy using IL-18 producing cells.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to practice the claimed invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3, 9, 12, 15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 9, 12, and 15 are indefinite because they are dependent on withdrawn claims. It is noted that claims 3, 9, 12, 15 are dependent on claims 1, 7, 10, and 13 respectively. For the sake of compact prosecution, the limitations of the claims have been considered in examining the elected invention. Applicants are advised to amend the claims to include these limitations in the elected claims.

Claim 3, 9, 10, 12, 15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: that the transplantation of the proliferated transformed tumor cells in the subject results in treatment of the tumor in the subject. It is noted that without the recitation of this step, it is not clear whether transplantation results in treatment or not.

10. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or

proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER